UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF TEXAS
MARSHALL DIVISION

ERFINDERGEMEINSCHAFT UROPEP GBR, Plaintiff, vs. ELI LILLY AND COMPANY, and BROOKSHIRE BROTHERS, INC., Defendants.	Court File No.: 2:15-cv-01202-WCB **JURY TRIAL DEMANDED**

DEFENDANTS ELI LILLY & CO.'S AND BROOKSHIRE BROTHERS, INC.'S MOTION FOR SUMMARY JUDGMENT OF NONINFRINGEMENT AND MEMORANDUM OF LAW IN SUPPORT THEREOF

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[1] All exhibits in support of Defendants' two summary judgment motions are compiled in a Joint Appendix and filed contemporaneously with these motions.

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Defendants Eli Lilly and Company and Brookshire Brothers, Inc. (collectively, "Lilly") hereby submit this Motion for Summary Judgment of Noninfringement and Memorandum of Law in Support Thereof, as to asserted claims 1 and 3 of U.S. Patent No. 8,791,124 (the "'124 Patent").

I. STATEMENT OF THE ISSUE TO BE DECIDED

If the term "inhibitor of phosphodiesterase (PDE) V" is governed by 35 U.S.C. § 112, ¶ 6, whether Defendants are entitled to summary judgment of noninfringement because no reasonable jury could find that Cialis® (tadalafil) is an equivalent structure of zaprinast or MY5445, or any other compound or compound class, disclosed in the '124 Patent for inhibiting PDE5.[2]

II. SUMMARY OF ARGUMENT

A. The Patent Act Establishes a *Quid Pro Quo* Bargain for Functional Claims.

Although a patentee may claim a functional result broadly, there is a *quid pro quo* bargain that accompanies such a claim. This bargain is reflected in at least two statutory sections of the Patent Act and is based on the underlying policy that a patentee's right to exclude cannot "overreach the scope of [its] contribution to the field of art as described in the patent specification"—lest the *quid pro quo* bargain at the heart of the Patent Act be upset. *Centocor Ortho Biotech, Inc. v. Abbott Labs*., 636 F.3d 1341, 1353 (Fed. Cir. 2011). First, the written description requirement "ensures that when a patent claims a genus by its function or result, the specification recites sufficient materials to accomplish that function—a problem that is particularly acute in the biological arts." *Ariad Pharmaceuticals, Inc. v. Eli Lilly and Co*., 598

[2] At the time the '124 patent was filed, the nomenclature for identifying a PDE enzyme interchangeably used either a Roman numeral or Arabic numeral to indicate the specific type of PDE enzyme—i.e., PDE1 or PDE I, PDE4 or PDE IV, or PDE5 or PDE V. Subsequently, the nomenclature has been clarified to refer to these PDE enzymes as PDE1, PDE2, PDE3, and so on. This Brief will use the more modern nomenclature of PDE5, etc.

F.3d 1336, 1323-34 (Fed. Cir. 2010) (*en banc*). This is the subject of Defendants' contemporaneously filed Motion for Partial Summary Judgment of Invalidity.

The present Motion is directed to the second way that the Patent Act statutorily enforces this *quid pro quo* bargain—through § 112, ¶ 6. Where, as here, the claim recites function (inhibiting PDE5) without reciting sufficient structure to perform that function, § 112, ¶ 6 applies and the scope of the claim is limited to "only the structure, materials, or acts described in the specification as corresponding to the claimed function and equivalents thereof." *Williamson v. Citrix Online, LLC*, 792 F.3d 1339, 1347 (Fed. Cir. 2015).

B. There Is No Evidence Demonstrating That Tadalafil Is Corresponding Or Equivalent To The Compounds Of The '124 Patent.

Tadalafil is not disclosed in the '124 Patent—not by name, not by empirical formula, not by chemical structure, and not by class. Thus, to avoid summary judgment of noninfringement, UroPep bears the burden to come forward with evidence that tadalafil is "equivalent" to structures disclosed in the '124 Patent as corresponding to the function of inhibiting PDE5. The only structures disclosed in the specification of the '124 Patent corresponding and clearly linked to that function, not otherwise excluded from the claim scope,[3] are zaprinast and MY5445.

UroPep cannot meet its burden of proving that tadalafil is an equivalent structure to either zaprinast or MY5445. No reasonable jury could find that tadalafil is equivalent to either zaprinast or MY5445—or, indeed, to any of the compounds or compound classes disclosed in the '124 Patent—such that the structural differences between these compounds are insubstantial.

[3] As discussed below, claim 1 of the '124 Patent was amended during prosecution to exclude eight compounds that were disclosed in the specification as PDE inhibitors, specifically labeled "b" and "d" – "j" in columns 2 through 4 of the patent. The '124 Patent also disclosed "quinazolines and their trimethoxy derivatives" and "pyrazolopyrimidones" at "k" and "l" of column 4. However, these are *classes* of compounds encompassing an unknown but extremely large group of compounds—only some of which might inhibit PDE5. Thus, the classes of compounds identified as "k" and "l" in the '124 Patent cannot be considered "corresponding structure" because there is no clear linkage to the function of inhibiting PDE5.

Tadalafil's properties—its interaction with PDE5, its potency and selectivity for PDE5, and its pharmacokinetic activity in the human body—emerge from its uniquely different structure. A chemical composition and its properties are inseparable. *In re Papesch*, 315 F.2d 381, 391, 137 USPQ 43, 51 (CCPA 1963) ("From the standpoint of patent law, a compound and all its properties are inseparable."). As UroPep's expert, Dr. Terrett, acknowledged, "[a]n individual compound has a unique chemical structure that confers the compound's pharmacological and physical properties, *and no alteration of the connections between the atoms is permitted as such change would redefine the identity of the compound*." Ex. 6, Declaration of Nicholas Terrett at ¶ 23 (emphasis added); App. at 0181.[4]

Tadalafil's unique structure, and the properties that structure confers, are substantially different from the properties of zaprinast or MY5445, each of which has a very different chemical structure (and thus very different properties) from tadalafil. Tadalafil's properties contribute to its unique position among all PDE5 inhibitors as the only drug on the market today that is approved by the FDA for the treatment of the signs and symptoms of BPH. In stark contrast, zaprinast and MY5445 were never clinically relevant, and none of the other disclosed compounds or classes of compounds has been approved for treatment of BPH.

Because no reasonable jury could find that tadalafil is an equivalent structure to the structures disclosed in the '124 Patent, summary judgment of noninfringement should be granted in favor of Defendants. "[T]he burden on the moving party may be discharged by 'showing'—that is, point out to the district court—that there is an absence of evidence to support the nonmoving party's case." *Exigent Tech., Inc. v. Altrana Solutions, Inc.*, 422 F.3d 1301, 1308 (Fed. Cir. 2006) (quoting *Celotex Corp. v. Catrett*, 477 U.S. 317, 325 (1986)).

[4] All exhibits in support of Defendants' two summary judgment motions are compiled in a Joint Appendix and filed contemporaneously with these motions.

III. LEGAL FRAMEWORK FOR DETERMINING WHETHER TADALAFIL IS EQUIVALENT STRUCTURE

A. Literal Infringement Requires The Accused Structure Perform The Identical Function And Be Identical Or Equivalent To Corresponding Structure In The Specification.

The first step in assessing literal infringement of a claim governed by Section 112, ¶ 6 is "a determination of the function of the means-plus-function limitation." *Medtronic, Inc. v. Advanced Cardiovascular Sys., Inc.*, 248 F.3d 1303, 1311 (Fed. Cir. 2001). Here, the function is to inhibit PDE5.

The next step is "to determine the corresponding structure disclosed in the specification and equivalents thereof." *Id*. A "structure disclosed in the specification is 'corresponding' structure only if the specification or prosecution history clearly links or associates that structure to the function recited in the claim." *Id*. The focus of the "corresponding structure" inquiry is not merely whether a structure is capable of performing the recited function, but rather whether the corresponding structure is "clearly linked or associated with the [recited] function." *Id*.

Literal infringement of a claim limitation governed by § 112, ¶ 6 requires that the accused structure perform the identical function recited in the claim and be identical or equivalent to the corresponding structure in the specification. *See, e.g., Chiuminatta Concrete Concepts, Inc. v. Cardinal Indus., Inc.*, 145 F.3d 1303, 1308 (Fed. Cir. 1998). Because tadalafil is indisputably not structure disclosed in the specification of the '124 Patent, the only question is whether tadalafil is an equivalent structure to that structure disclosed in the '124 Patent for inhibiting PDE5.

B. The Proper Test For Equivalents Under § 112, ¶ 6 Is Whether The Differences Between The Structure In The Accused Device And Any Disclosed In The Specification Are Insubstantial.

Section 112, ¶ 6 rules out the possibility that any and every compound that inhibits PDE5 literally satisfies the claim. *Chiuminatta*, 145 F.3d at 1309. Rather, to determine whether the

accused compound, tadalafil, is "equivalent" structure to the disclosed compounds in the '124 Patent, "[t]he proper test is whether the differences between the structure in the accused device and any disclosed in the specification are insubstantial." *Id.* An "insubstantial" difference is one that adds "nothing of significance" to the structure disclosed in the patent specification. *Id.* (quoting *Valmont Indus., Inc. v. Reinke Mfg. Co., Inc.*, 983 F.2d 1039, 1043 (Fed. Cir. 1993).

C. The Question Of Equivalents Is Amenable To Summary Judgment Where There Is No Evidence Of Insubstantial Differences And No Reasonable Jury Could Find Equivalence.

UroPep bears the ultimate burden of proving that tadalafil is equivalent to the disclosed corresponding structure. *Applied Medical Resources Corp. v. U.S. Surgical Corp.*, 448 F.3d 1324, 1333 (Fed. Cir. 2006). Thus, although the question of "equivalents" under § 112, ¶ 6 is a fact question, the Supreme Court and Federal Circuit both have emphasized that trial courts should direct judgment on the issue of equivalence where the patentee cannot meet its burden and "the evidence is such that no reasonable jury could determine two elements to be equivalent." *Dawn Equipment Co. v. Kentucky Farms Inc.*, 140 F.3d 1009, 1017 (Fed. Cir. 1998) (quoting *Warner–Jenkinson Co., Inc. v. Hilton Davis Chem. Co*., 520 U.S. 17, 39 n. 8 (1997)).

The structural differences between tadalafil, zaprinast and MY5445 are not insubstantial; this is dispositive as to the question of whether tadalafil can be considered an equivalent to zaprinast or MY5445 (or, indeed, any of the compounds in the patent). *Chiuminatta*, 145 F.3d at 1309. To the contrary, the evidence demonstrates that tadalafil binds to PDE5 differently, has different potency and selectivity for PDE5, and acts within the body differently. In short, UroPep cannot meet its burden. *JVW Enterprises, Inc. v. Interact Accessories, Inc.*, 424 F.3d 1324, 1333 (Fed. Cir. 2005) (to show "insubstantial" differences, the structure in the accused device must perform the claimed function in substantially the same way to achieve substantially the same result as the structure in the written description).

IV. STATEMENT OF UNDISPUTED MATERIAL FACTS ("SMF")

A. The Disclosed Corresponding Structure For Inhibiting PDE5: Zaprinast And MY5545.

1. The specification of the '124 Patent discloses "[p]referred inhibitors of PDE I, PDE IV and PDE V". Ex. 1, '124 Patent, col. 2:28-4:47; App. at 0003.

2. The specification of the '124 Patent does not identify which of the disclosed compounds or classes of compounds inhibit PDE1 versus PDE4 versus PDE5. *Id.* at Abstract; col. 1:44-47; 2:6-13; App. at 0002-0003.

3. The specification further states: "Therefore, the subject matter of the invention is the use of specific inhibitors of sPDE I, sPDE IV and sPDE V in the prophylaxis and treatment of prostatic diseases…." *Id.* at col. 2:17-19; App. at 0003.

4. Ten of the "[p]referred inhibitors of PDE I, PDE IV and PDE V" are identified by chemical name or structure, and are labeled "a" through "j". *Id.* at col. 1:29-4:45; App. at 0003.

5. Of these ten compounds labeled "a" through "j" in the specification, eight of them—specifically, compounds labeled "b" and "d"-"j" in the specification—are expressly excluded from Claim 1 of the '124 Patent.[5] *Id.* at col. 8:18-47; App. at 0006.

6. The '124 Patent also discloses two classes of compounds, which are labeled as "k" ("quinazolines and their trimethoxy derivatives") and "l" ("pyrazolopyrimidones"). *Id.* at col. 4:46-47; App. at 0004.

7. Compounds "d" and "f" are within the class of quinazolines, but are excluded from the scope of Claim 1 of the '124 Patent. Ex. 3, Declaration of David P. Rotella, Ph.D. In

[5] The compound *1-methyl-3-propyl-6-(5-(N-(4-methylmorpholino)sulfonyl)-2-ethoxyphenyl)pyrazole[4,5]pyrimidin-4(5H)one*, or "sildenafil" (compound "g"), is excluded ***twice*** from the language of Claim 1 of the '124 Patent.

Support of Defendants' Motion for Summary Judgment of Noninfringement ("Rotella Noninfringement Decl.") at ¶ 37; App. at 0049-50.

8. Compounds "g" and "j" are within the class of pyrazolopyrimidones, but are excluded from the scope of Claim 1 of the '124 Patent. *Id.* at ¶ 40; App. at 0050-0051.

9. The '124 Patent does not identify any other members of the classes of quinazolines or pyrazolopyrimidones. *Id.* at ¶ 41; App. at 0050.

10. The number of compounds that would fall within the class of quinazolines and their trimethoxy derivatives and the class of pyrazolopyrimidones is unknowable but extremely large. *Id.* at ¶¶ 34-43; App. at 0048-0051.

11. Dr. Terrett testified that the class of quinazolines alone encompasses "billions" of compounds. Ex. 5, Deposition of Nicholas Terrett ("Terrett Dep.") at p. 69:3-11; App. at 0156. Compounds within the class of quinazolines and their trimethoxy derivatives and the class of pyrazolopyrimidones would have diverse molecular structures that would affect their biological activity. Ex. 3, Rotella Noninfringement Decl. at ¶ 34-43; App. at 0048-0051.

12. Not all compounds within the class of quinazolines and their trimethoxy derivatives and the class of pyrazolopyrimidones would inhibit PDE5. *Id.*; *see also* Ex. 5, Terrett Dep. at p. 69-70; App. at 0156-0157.

13. Other than compounds "d", "e", "g" and "j"—which are excluded from the scope of Claim 1—the '124 Patent does not disclose any compound structure within the classes of "quinazolines and their trimethoxy derivatives" or "pyrazolopyrimidones", or describe any common structure of compounds within these classes, for the function of inhibiting PDE5. Ex. 3, Rotella Noninfringement Decl. at ¶ 44; App. at 0051-0052.

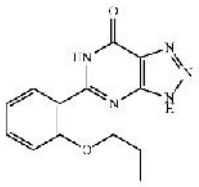
14. The only two chemical compound structures linked to inhibiting PDE5 that are described by structure and not excluded from the scope of the claims of the '124 Patent are:

a. zaprinast (disclosed as compound "a", Ex. 1, '124 patent, col. 2:29-40); App. at 0003; and

b. MY5445 (disclosed as compound "c", Ex. 1, '124 Patent, col. 3:1-18); App. at 0004.

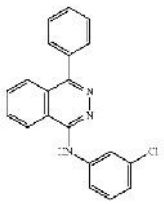
Id. at ¶ 32; App. at 0047; *see also id.* at ¶¶ 30-31; App. at 0046.

15. Zaprinast has the chemical name 2-(2-propoxyphenyl)-8-azapurin-6-one and empirical formula of $C_{13}H_{13}N_5O_2$. Its structure is shown below:



Id. at ¶ 52; App. at 0054; Ex. 1, '124 Patent at col. 2:29-40; App. at 0003.

16. MY5445 has the chemical name 1-(3-chlorophenylamino)-4-phenylphthalazine and empirical formula $C_{20}H_{14}ClN_3$. Its structure is shown below:



Ex. 3, Rotella Noninfringement Decl. at ¶¶ 55-56; App. at 0055-0056; Ex. 1, '124 Patent at col. 3:1-18; App. at 0004.

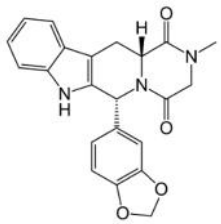
B. The Structure Of Tadalafil.

17. The name of tadalafil is 6R-trans)-6-(1,3-benzodioxol-5-yl)- 2,3,6,7,12,12a-hexahydro-2-methyl-pyrazino [1', 2':1,6] pyrido[3,4-b]indole-1,4-dione. Ex. 3, Rotella Noninfringement Decl. at ¶ 64; App. at 0058.

18. An alternative name for tadalafil is (6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylene dioxyphenyl)pyrazino [2', 1' : 6, 1] pyrido [3, 4-b] indole -1,4-dione. *Id*.

19. The empirical formula of tadalafil is $C_{22}H_{19}N_3O_4$. *Id.* at ¶ 65; App. at 0058.

20. The chemical structure of tadalafil is shown below:



Id. at ¶ 66; App. at 0058.

21. The chemical structure of tadalafil and its ability to inhibit PDE5 was disclosed in a PCT patent Application no. PCT/EP95/00183, published on July 27, 1995—nearly two years before the filing date of the earliest priority application asserted for the '124 Patent. *Id.* at ¶ 63; App. at 0058; Ex. 8, PCT Application No. PCT/EP95/00183; App. at 0198-0285.

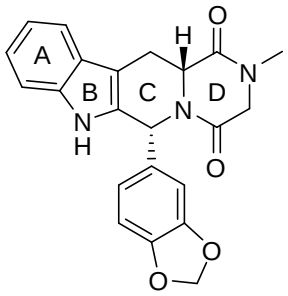
22. Tadalafil is not disclosed in the '124 Patent by name, chemical structure, empirical formula, or compound class (beta carbolines) to which tadalafil is a member. *Id.* at ¶¶ 62, 68-71; App. at 0058-0059.

C. Tadalafil Has A Uniquely Different Structure From Other Disclosed Compounds.

23. The chemical structure of tadalafil is substantially different from the structures of zaprinast and MY5445, as well as all the other disclosed compounds and classes of compounds identified in the '124 Patent. The particular structure of tadalafil, compared to the structures of the disclosed compounds, can influence enzyme binding characteristics, such as selectivity and potency of the compound, as well as physical properties and pharmaceutical properties (e.g. pharmacokinetics, oral bioavailability, water solubility and melting point). *Id.* at ¶ 83; App. at 0065-0066; *see also id.* at ¶¶ 76-78, 92-121; App. at 0061-0063, 0068-0081.

24. The differences between the structure of tadalafil compared to zaprinast and MY5445, as well as other disclosed compounds or classes of compounds, are described below:

a. The structure of tadalafil comprises a linearly fused tetracyclic core (i.e., a core of 4 fused rings) as indicated by the ABCD nomenclature in the figure below. The AB ring system is analogous to an indole ring system and is 2,3 fused. The CD ring system is non-aromatic and includes four sp^3 carbons. The CD ring system also includes two endocyclic tertiary amides. The C ring has a 1,3 benzodioxole substituent. The D ring nitrogen is methyl substituted. In addition, the core structure of tadalafil (the fused rings A, B, C, and D) is composed of both aromatic and non-aromatic portions.

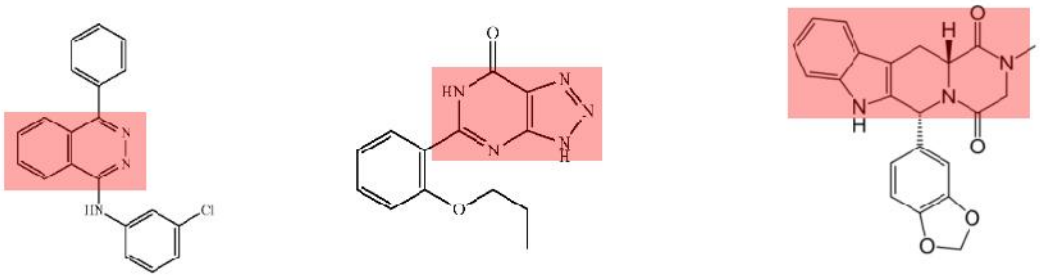


b. In contrast to the four ring structure of tadalafil, the core structures of zaprinast and MY5445 are bicyclic, in that they are composed of two fused rings.

c. The core structures of all of the compounds disclosed in the '124 Patent, quinazolines and their trimethoxy derivatives and the class of pyrazolopyrimidones, are either moncyclic (one ring) or bicyclic (two fused rings).

d. The tadalafil CD ring system also shows a bridgehead nitrogen (i.e., a nitrogen atom that exists in two fused rings). Every other ring system of the disclosed compounds in the '124 Patent, including zaprinast and MY5445, have only bridgehead carbons.

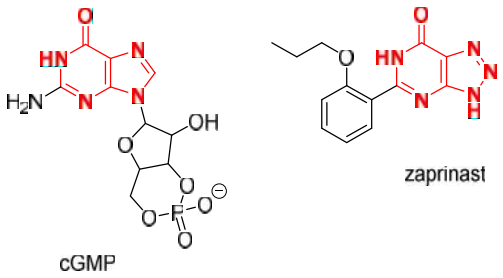
e. The differences in the core structures of tadalafil compared to MY5445 and zaprinast is shown below.



MY5445 Zaprinast Tadalafil

f. The '124 Patent does not disclose any compounds or classes of compound that have a tetracyclic (four fused ring) core structure.

g. The bicyclic core structure of zaprinast is similar to the bicyclic core structure of cGMP, as shown below by the similarity between the two nitrogen-containing fused ring portions of their structures (highlighted below):



h. The core structure of tadalafil lacks a bicyclic core structure like that in cGMP.

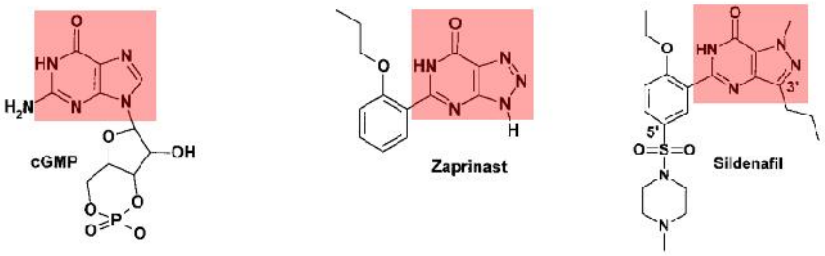
i. The core structure of tadalafil is composed of both aromatic and non-aromatic portions. In contrast, the core structures of both zaprinast and MY5445 are composed of only aromatic ring systems.

Ex. 3, Rotella Noninfringement Decl. at ¶¶ 84-91; App. at 0066-0068; *see also id.* at ¶¶ 32-44, 51-67; App. at 0047-0052, 0054-0059.

25. An individual compound has a unique chemical structure that confers the compound's pharmacological and physical properties. Any alteration or change in structure redefines the identity of the compound. *Id.* at ¶ 76; App. at 0061,

26. Even structurally similar compounds have unique chemical structures that may confer different pharmacological and physical properties. For example, a compound known as sildenafil (the branded drug Viagra) is disclosed in the '124 Patent as a preferred inhibitor of PDE1, PDE4 and PDE5 inhibitor. '124 Patent, col. 2:28-29, col. 3:48-64 (compound "g"); App. at 0004. Sildenafil was synthesized by Pfizer scientists, including Dr. Terrett, by using zaprinast as a precursor compound. *Id.* at ¶ 59, 61; App. at 0056-0057.

27. Like zaprinast, the core structure of sildenafil has two fused rings. Like zaprinast, the core structure of sildenafil is similar to the core structure of cGMP, as highlighted and shown below:



Id. at ¶ 61; App. at 0057.

28. Notwithstanding these similarities, the potency of sildenafil for PDE5 is approximately 13 times higher than zaprinast and even higher than that of MY5445. *Id.*

29. Sildenafil (compound "g" from the patent) is expressly excluded from the scope of Claim 1 of the '124 Patent. Ex. 1, '124 Patent, claim 1; App. at 0006.

D. Tadalafil Binds To PDE5 Differently Than Other Disclosed Compounds.

30. There is no evidence in the scientific literature that zaprinast interacts with, or binds to, PDE5 in the same way as tadalafil. To the contrary, given the differences between the structure of tadalafil and zaprinast and the similarity of structure between zaprinast and sildenafil, it would be reasonably expected that tadalafil binds to PDE5 differently than zaprinast. Rotella Noninfringement Decl. at ¶ 97-105; App. at 0071-0074.

31. There is no evidence in the scientific literature that MY5445 interacts with, or binds to, PDE5 in the same way as tadalafil. Tadalafil has a comparatively rigid tetracyclic core structure with a single substituent off its core. In contrast, MY5445 has a different bicyclic core with two substituents appended to its core. Based upon the structural differences between

tadalafil and MY5445, it would be reasonably expected that tadalafil binds to PDE5 differently from MY5445. *Id.*

32. X-ray crystallography (which obtains a molecular level picture of the specific interactions between a small molecule and a protein) is a known method to determine how a compound binds to an enzyme such as PDE5. *Id.* at ¶ 101; App. at 0072.

33. The scientific literature has used x-ray crystallography to show how tadalafil binds to PDE5. UroPep has not produced any report using x-ray crystallography, or any other method, to show how zaprinast or MY5445 bind to PDE5, and Lilly is not aware of any such reports. However, x-ray crystallography has been used to show how sildenafil binds to PDE5 in comparison to tadalafil. The literature reports that tadalafil binds to PDE5 differently than sildenafil. Specifically, PDE5 has a pocket-shaped catalytic site, which is one place where PDE5 inhibitors can bind. The evidence from the studies conducted by Sung et al. showed that tadalafil binds in this pocket differently from all known PDE5 inhibitors in which studies have been conducted, including sildenafil. *Id.* at ¶ 102-103; App. at 0072-0073.

34. Another method to evaluate how an inhibitor binds to an enzyme looks at the interaction with specific amino acid residues at the binding location of the enzymatic protein. Again, Lilly is not aware of a study using this method to show how zaprinast or MY5445 bind to PDE5. However, a study conducted by Zoraghi et al. using this method demonstrated that tadalafil binds to PDE5 differently from sildenafil in that these two compounds do not interact with the same amino acids in PDE5 in the same way. Given the structural similarity between sildenafil and zaprinast, and the structural differences both compounds have with tadalafil, it would be reasonable to expect that zaprinast binds to PDE5 differently than tadalafil. *Id.* at ¶ 104; App. at 0073-0074.

35. There is no evidence in the scientific literature that MY5445 interacts with, or binds to, PDE5 in substantially the same way as tadalafil. Given the structural differences with tadalafil, it would be reasonable to expect that MY5545 binds to PDE5 differently than tadalafil. Tadalafil has comparatively rigid tetracyclic core structure with a single substituent off its core. In contrast, MY5545 has a different bicyclic core with two substituents appended to its core. *Id.* at ¶ 105; App. at 0074; *see also id.* at ¶¶ 97-104; App. at 0071-0073.

E. Tadalafil Has Substantially Different Potency And Selectivity Compared To Other Disclosed Compounds.

36. The more tightly a drug binds to its receptor (i.e., the PDE5 enzyme in this case), the higher the affinity it is considered to have for that receptor. This concept of affinity (sometimes referred to as potency) can be assessed by measuring the concentration of a particular compound *in vitro* that inhibits PDE5 activity by 50% —which is known as the IC_{50}. Highly potent drugs are expected to have affinities (IC_{50} values) in the low nanomolar (less than 20 nM) range. IC_{50} values can be used to compare the affinity of compounds for a target or targets. *Id.* at ¶ 109; App. at 0075-0076.

37. The higher the affinity of a drug for a given receptor relative to other potential receptor sites, the greater the selectivity of the drug. Thus, selectivity measures the affinity of a drug to PDE5 relative to other PDEs. Selectivity of a compound for a specific receptor or desired site of action is a key factor in determining its side-effect profile. Selectivity is defined as the ratio between the IC_{50} for a given PDE and the IC_{50} for PDE5. *Id.* at ¶ 110; App. at 0076.

38. Tadalafil's potency for PDE5 and selectivity for PDE5 compared to other PDEs is very different compared to what has been reported in the literature for zaprinast and MY5445. *Id.* at ¶ 106-117; App. at 0074-0080.

39. The table below from the Journal of Medicinal Chemistry shows the differences in tadalafil's potency and selectivity for PDE5 compared to zaprinast. *Id.* at ¶ 112; App. at 0077.

Table 2. Cyclic Nucleotide Selectivity Profile of the 11 PDE Family Members[a]

PDE family	pharmacological classification	cyclic nucleotide substrates	inhibitors	K_i or (IC_{50})
PDE1	Ca^{2+}/CAM stimulated PDE	cAMP and cGMP	vinpocetine	14 μM
			zaprinast	(6 μM)[37]
			sildenafil	(350 nM)[38]
PDE2	cGMP-stimulated PDE	cAMP and cGMP	EHNA	1 μM
			Bay 60-7550	(4.7 nM)[56]
PDE3	cGMP-inhibited PDE	cAMP > cGMP	cilostamide	20 nM
			milrinone	150 nM
			zardaverine	(0.5−2 μM)
PDE4	high affinity, rolipram-sensitive cAMP-specific PDE	cAMP	rolipram	1 μM
			roflumilast	(0.8 nM)[45]
			cilomilast	(120 nM)[45]
			zardaverine	(0.8−4 μM)
PDE5	cGMP-specific PDE	cGMP	zaprinast	130 nM
			sildenafil	10 nM
			vardenafil	1 nM
			tadalafil	10 nM
PDE6	photoreceptor cGMP-specific PDE	cGMP	zaprinast	400 nM
			dipyridamole	125 nM
			sildenafil	50 nM
			vardenafil	(11 nM)[38]
			tadalafil	(2 μM)
PDE7	high-affinity, rolipram-insensitive cAMP-specific PDE	cAMP	IBMX	4 μM
			dipyridamole	600 nM
PDE8	high-affinity and IBMX-insensitive cAMP-specific PDE	cAMP	dipyridamole	9 μM
PDE9	high-affinity cGMP-specific PDE	cGMP	zaprinast	35 μM
PDE10	cAMP-inhibited cGMP PDE	cAMP < cGMP	dipyridamole	1 μM
			zaprinast	(22 μM)[36]
PDE11	dual specificity cGMP-binding PDE	cAMP and cGMP	zaprinast	12 μM
			dipyridamole	0.4 μM
			tadalafil	60 μM

40. The data in this table shows:

i. Tadalafil is approximately 13 times more potent to PDE5 than zaprinast.

ii. Tadalafil is more than 200 times more selective to PDE5 versus PDE6 than zaprinast.

iii. Zaprinast shows affinity for PDE1, PDE9, and PDE 10; Tadalafil has no measurable affinity for those PDEs.

iv. Tadalafil is five times more potent for PDE 11 than zaprinast.

Id. at ¶ 113; *see also id.* at ¶ 114; App. at 0078.

41. The molecular structure of the PDE5 and PDE6 enzymes are closely related; thus, it is difficult for any compound to have affinity for PDE5 without having significant affinity for PDE6. Due its different structure, however, tadalafil is able to differentiate between PDE5 and PDE6, and has been measured to have significant selectivity to PDE5 versus PDE6, and thus

avoiding the visual disturbances and side effects commonly associated with inhibition of PDE6. *Id.* at ¶ 116; App. at 0079.

42. For example, sildenafil's selectivity for PDE5 compared to PDE6 is much different than tadalafil. Sildenafil is has significant affinity for PDE6; tadalafil does not. Sildenafil's selectivity to PDE6 may contribute to reported visual disturbances associated with that drug, and has required that visual disturbances be identified on the label of Viagra® (sildenafil) as a side effect. *Id.* at ¶ 115; App. at 0078-0079.

43. There is no evidence that tadalafil's affinity and selectively profile is the same or substantially the same as zaprinast. *Id.* at ¶ 115; App. at 0078-0079.

44. There is little reported data on the enzyme inhibition profile of MY5445, and no evidence tadalafil's affinity and selectively profile is similar to MY5445. At least one study reports that zaprinast was four-fold more potent for PDE5 than MY5445. Given that tadalafil has been reported to be approximately 13-fold more potent for PDE5 than zaprinast, it is reasonable to conclude that tadalafil is significantly more potent for PDE5 than MY5445. *Id.* at ¶ 117; App. at 0079-0080; *see also id.* at ¶¶ 112-114; App. at 0077-0078.

45. There is no evidence that tadalafil's selectively profile is the same or substantially the same as MY5445. Rather, given its structural differences with tadalafil, it would be reasonable to expect that MY5545 to have a different selectivity profile from tadalafil. *Id.* at ¶¶ 112-114, 117; App. at 0077-0080.

46. There is no evidence that tadalafil's affinity and selectively profile is the same or substantially the same as any of the compounds disclosed in the '124 Patent. Given their structural differences with tadalafil, it would be reasonable to expect that the compounds

referenced in the '124 Patent have different affinity and selectively profiles from tadalafil. *Id.* at ¶ 118; App. at 0080.

F. Tadalafil's Pharmacokinetic Results Are Different From Other Disclosed Compounds.

47. Pharmacokinetic data are available for tadalafil and sildenafil, since both compounds are marketed drugs. However, because zaprinast and MY-5445 were never commercially marketed, there is limited *in vivo* human pharmacokinetic data for zaprinast and no known reported *in vivo* human pharmacokinetic data for MY5445. There is no evidence that the pharmacokinetic data for zaprinast and MY5445 would be the same or substantially the same as tadalafil. *Id.* at ¶ 120; App. at 0080.

48. Given the substantially different chemical structures as compared to tadalafil (e.g., zaprinast and MY5445 both have bicyclic core structures, whereas tadalafil has a tetracyclic core structure), the pharmacokinetic data for either zaprinast or MY5445 would be expected to differ in numerous respects from tadalafil's pharmacokinetic data. *Id.*

49. The pharmacokinetic data of tadalafil compared to sildenafil is demonstrative of the areas where one would expect to see tadalafil substantially differ from other compounds, including zaprinast and MY5445:

a. Tadalafil has a longer T_{max} compared to sildenafil.

b. Tadalafil has greater bioavailability compared to sildenafil.

c. Tadalafil has a greater half-life ($t_{1/2}$) (17.5 hours) compared to sildenafil (3.7 hours hours). As reported by Corbin et al., "a PDE5 inhibitor such as tadalafil with a long $t_{1/2}$ is likely to have a greater AUC than the PDE5 inhibitors with a short $t_{1/2}$."

d. Tadalafil has a greater AUC (area under curve) compared to sildenafil.

Id. at ¶ 121; App. at 0081.

50. Tadalafil currently is the only drug on the market today approved by the Federal Food and Drug Administration ("FDA") for the treatment of the signs and symptoms of benign prostatic hyperplasia ("BPH"). *Id.* at ¶ 58; App. at 0056.

51. The pharmacokinetic profile of tadalafil has critical clinical importance in its use for the treatment of the signs and symptoms of benign prostatic hyperplasia ("BPH"). Tadalafil's significantly longer half-life and greater AUC may be valuable to longer therapeutic effect, which is important for managing conditions that require continuous drug activity, such as BPH. *Id.* at ¶ 122; App. at 0081.

V. ARGUMENT

A. The Term "Inhibitor Of Phosphodiesterase (PDE) V" Is Purely Functional: It Lacks Structure Sufficient To Perform The Function Of Inhibiting PDE5 And Is Therefore Governed By Section 112, ¶ 6.

The question of whether the claim term "inhibitor of phosphodiesterase (PDE) V" is purely functional and lacks any recitation of structure sufficient to inhibit PDE 5 has been briefed and argued to the Court. It bears repeating that UroPep's own expert acknowledged that there is no common structure for compounds able to inhibit PDE5. As stated by Dr. Terrett, "it is the ability of these compounds to inhibit PDE V that defines them as a group, rather than a common structural feature or similarity." Ex. 6, Terrett Decl. at ¶ 23; App. at 0181; *see also* Ex. 5, Terrett Dep., p. 25:6-22; App. at 0145.

Thus, even if the person of skill in the art would understand the term "inhibitor" to be a compound, the scope of the genus of "compounds" that might function to inhibit PDE5 is unknowable. Consequently, claim 1 of the '124 Patent recites "function without reciting sufficient structure for performing that function." *Williamson*, 792 F.3d at 1349 (citations omitted).

B. The Only Disclosed Structures Corresponding And Clearly Linked To Inhibiting PDE5—Not Otherwise Excluded From The Claims—Are Zaprinast And MY5445.

The only structure disclosed in the specification of the '124 Patent corresponding and clearly linked to performing the function of inhibiting PDE5 are "a" (zaprinast) and "c" (MY5445). SMF ¶¶ 1-14.

The eight compounds disclosed as "b" and "d"-"j" in the '124 Patent are expressly excluded from the claims of the '124 Patent. SMF ¶ 5. During prosecution of the '124 Patent, the Examiner rejected the pending claims on multiple grounds including nonstatutory double patenting in view of claims 1-5 of the '061 Patent and as anticipated or rendered obvious in view of art which taught the use of PDE5 inhibitors for various diseases associated with the prostate. Ex. 49, '124 Patent File History, at JX_124_FH0107-214; App. at 0864-0908. In response, UroPep amended its claims to recite a "negative" Markush group, *i.e.,* a claim directed to all "inhibitors of phosphodiesterase (PDE) V" but excluding eight compounds identified in the specification as compounds "b" and "d" through "j". *Id.* at JX_124_FH0217-221; App. at 0910-0914. The double patenting rejection was maintained by the Examiner, *id.* at JX_124_FH_0231-232; App. at 0921-0922; consequently, UroPep filed the terminal disclaimer and the claims of the '124 Patent were allowed, *id.* at JX_124_FH0228-240; App. at 00918-0926.

Prosecution history estoppel bars a patentee from asserting a scope of equivalency surrendered during prosecution. *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1323-24 (Fed. Cir. 2009). In addition, "[j]ust as prosecution history estoppel may act to estop an equivalence argument under the doctrine of equivalents, positions taken before the PTO may bar an inconsistent position on claim construction under § 112, ¶ 6." *Alpex Computer Corp. v. Nintendo Co.*, 102 F.3d 1214, 1221 (Fed. Cir. 1996). "Thus, prosecution history disclaimer may limit the range of equivalent structures that fall within the scope of a means-plus-function

limitation." *Regents of University of Minnesota v. AGA Medical Corp.*, 717 F.3d 929, 942 (Fed. Cir. 2013). UroPep's amendment to claim 1 of the '124 Patent to expressly exclude compounds "b" and "d" through "j" from the scope of the claims thus bars UroPep from asserting equivalency for the compounds that were expressly excluded from the scope of the asserted claims during prosecution.

The '124 Patent also discloses two broad classes of compounds, "quinazolines and their trimethoxy derivatives" (labeled "k" in the patent) and "pyrazolopyrimidones" (labeled "l" in the patent). SMF ¶ 6. Disclosure of these two classes at most identifies a common core for an unknowable but very large number of distinct compounds within the classes. SMF ¶¶ 6-13. Dr. Terrett testified that the class of quinazolines alone encompasses "billions" of compounds. SMF ¶¶ 10-11; Ex. 5, Terrett Dep., p. 69:3-11; App. at 0156. Some of these compounds may inhibit PDE5, and some may not. *Id.* Thus, these two classes of compounds cannot constitute "corresponding" structure because they are not clearly linked to the inhibition of PDE5. A "structure disclosed in the specification is 'corresponding' structure only if the specification or prosecution history clearly links or associates that structure to the function recited in the claim." *Medtronic*, 248 F.3d at 1311. Whether structure is "corresponding" is not merely whether a structure is capable of performing the recited function, but rather whether the corresponding structure is "clearly linked or associated with the [recited] function." *Id*.

Moreover, two of the *excluded* compounds ("d" and "f") are from the class of quinazolines, and another two of the *excluded* compounds ("g" and "i") are from the class of pyrazolopyrimidones. SMF ¶¶ 7-8. UroPep's amendment to the claims to expressly exclude these compounds within the classes of quinazolines and pyrazolopyrimidones bars UroPep from now claiming equivalents based upon the classes. "[T]he concept of equivalency cannot embrace

a structure that is specifically excluded from the scope of the claims." *Dolly, Inc. v. Spalding & Evenflo Cos., Inc.*, 16 F.3d 394, 400 (Fed. Cir. 1994).

In any event, for all the reasons discussed herein that tadalafil cannot be considered "equivalent" structure to zaprinast or MY5445 (e.g., different structure, different potency, different selectivity, and different pharmacokinetic profile), tadalafil also cannot be considered "equivalent" structure to any of the other disclosed compounds or classes of compounds. SMF ¶¶ 21-51.

C. No Reasonable Jury Could Find That Tadalafil Has "Equivalent" Chemical Structure To Zaprinast And MY5445 (Or Any Of The Other Disclosed Compounds Or Classes Of Compounds).

No reasonable jury could find that tadalafil is an "equivalent" structure of zaprinast or MY5445, or any of the other disclosed compounds or classes of compounds. The molecular structure of tadalafil is substantially different than the structure of zaprinast and MY5445. SMF ¶¶15-24. Even a non-chemist is able to see the substantial structural differences between tadalafil, zaprinast, and MY5445.

The core structure of tadalafil—which influences its biological and pharmacological activity—is substantially different than the core structure of zaprinast and MY5445. SMF ¶¶ 15-24. Tadalafil is composed of a linear core structure of four fused rings. *Id.* Both zaprinast and MY5445 have a core structure of only two fused rings. *Id.*

The differences in core structures are not insubstantial. Tadalafil's tetracyclic core incorporates chirality (i.e., a carbon atom with four different groups attached), while zaprinast and MY5445 have different, achiral bicyclic cores. Tadalafil's unique core structure provides a substantially different template for interaction with PDE5. *Id.*; *see also* Ex. 3, Rotella Noninfringement Decl. at ¶ 105; App. at 0074.

The arrangement and nature of functional groups and heteroatoms (i.e., atoms other than carbon) in each structure are also different. SMF ¶ 15-24; Ex. 3, Rotella Noninfringement Decl. at ¶ 105. For example, the specific fragments attached to the core project from distinct points on each core and are different. *Id.* Tadalafil has a methyl group bonded to nitrogen in the D ring and a benzodioxole ring bonded to the C ring with specific stereochemistry. *Id.* In contrast, neither zaprinast nor MY5445 have an N-methyl substituent, a benzodioxole ring, or a chiral carbon. Zaprinast has a single fragment attached to its core, an alkoxy-substituted aromatic ring. *Id.* MY5445 has two aromatic rings attached to its core-one by a nitrogen atom and the other via a direct bond between two aromatic rings. *Id.* These differences in structure also are not insubstantial; the different chemical structures contribute to the substantial difference in IC_{50} values between these compounds, which is evidenced by the fact that tadalafil has measurably higher affinity for PDE5 compared to either MY5445 or zaprinast. *Id.*; *see also* SMF ¶¶ 25, 36-46.

Tadalafil's tetracyclic core structure is very different from all of the core structures of all of the compounds and compound classes disclosed in the '124 Patent. SMF ¶ 24. Tadalafil's four fused rings was unique among PDE5 inhibitors when the '124 Patent was filed; however, every compound disclosed in the '124 Patent has only one ring or two fused rings in their core. *Id.* This fundamental difference in core structures has a direct impact on the way the compound interacts in the human body (*in vivo*), the way PDE5 may be inhibited, and any efficacy of side effects that may result from taking the compound pursuant to the method of treatment or prophylaxis of BPH. Thus, UroPep's equivalence case fails as a matter of law. *Id.* at ¶¶ 23-51.

D. Tadalafil's Uniquely Different Structure Contributes To Its Different Binding Interaction With PDE5, Different Enzyme Inhibition Profile, And Different Pharmacokinetic Profile—Any Of Which Demonstrates Non-Equivalency.

As tadalafil is nowhere disclosed in the '124 Patent, it is UroPep's burden under § 112, ¶ 6 to come up with some evidence demonstrating that tadalafil is nonetheless an equivalent structure to those disclosed in the '124 Patent (and not disclaimed). UroPep cannot meet its burden of showing that the structure is substantially the same. UroPep also cannot meet its burden of showing that tadalafil binds to PDE5 in substantially the same way as zaprinast or MY5445, or achieves substantially the same results as zaprinast or MY5445. To the contrary, the evidence in the record and scientific literature demonstrates that the differences between the structure of Tadalafil and the structures of the other compounds, including zaprinast and MY5445, are substantial. *Id.* at ¶¶ 23-51.

One of ordinary skill in the art would know that any compound able to inhibit PDE5 has its own set of unique pharmacological characteristics based on its specific molecular structure, enzyme inhibition profile and pharmacokinetic properties. SMF ¶ 25; *see also* Ex. 3, Rotella Noninfringement Decl. at ¶¶ 92, 94; App. at 0068-0069. The specific structure of a PDE5 inhibitor will affect how it binds to PDE5. *Id.* Different chemical structures influence and contribute to binding interaction differences, and as the chemical structures of two compounds diverge, so do the nature of these interactions. *Id.* These divergences between tadalafil and the compounds disclosed in the '124 Patent are discussed below.

1. Due To Its Uniquely Different Structure, Tadalafil Interacts With The PDE5 Enzyme In A Substantially Different Way

Due to its uniquely different molecular structure, the scientific literature demonstrates that tadalafil interacts with, and binds to, the PDE5 enzyme in a different way from other PDE5 inhibitors. SMF ¶¶ 30-35; *see also* Ex. 3, Rotella Noninfringement Decl. at ¶¶ 97-105; App. at

0071-0074. There is no evidence that zaprinast, MY5445, or any other compound disclosed in the '124 Patent would be an exception to this rule. *Id.* To the contrary, all available evidence indicates that zaprinast, MY5445, or any other compound disclosed in the '124 Patent interacts with, and binds to, the PDE5 enzyme in a different way from tadalafil. *Id.*

There is no known enzyme interaction data in the scientific literature for zaprinast. However, a person of ordinary skill in the art would know that zaprinast is structurally similar to sildenafil (excluded compound "g"). SMF ¶¶ 26-30. Both zaprinast and sildenafil have a bicyclic core structure of two fused-rings that is similar to the core structure of cGMP. *Id.* In contrast, tadalafil's linear and more rigid core structure of four fused rings is not similar at all to the structure of cGMP. SMF ¶ 24; *see also* Ex. 3, Rotella Noninfringement Decl. at ¶¶ 97-105; App. at 0071-0074. Therefore, a person of ordinary skill in the art would reasonably expect that tadalafil would interact with PDE5 differently from zaprinast at least to the same extent as sildenafil. SMF ¶¶ 26-30, 33-35.

There also is no known enzyme interaction data published in the scientific literature for MY5445. However, given the vastly different structures of tadalafil and MY5445, it would also be reasonable to expect that tadalafil would bind to PDE5 differently than MY5445. SMF ¶¶ 31, 33-35.

2. Due to Its Uniquely Different Structure, Tadalafil Achieves Substantially Different Results In Its Potency For PDE5

UroPep also cannot meet its burden showing that tadalafil achieves substantially the same result as zaprinast, MY5445, or any other compound disclosed in the '124 Patent with regard to the inhibition of PDE5 for the prophylaxis or treatment of BPH. Tadalafil is the only PDE5 inhibitor approved for treatment of BPH. SMF ¶ 50. It received that approval in part because of the results that it can achieve in the human body based upon its unique chemical structure. SMF

¶ 51. There is no evidence that any of the compounds disclosed in the '124 Patent would achieve the same results; rather, the scientific literature strongly suggests they would not.

The affinity (or potency) of a compound to inhibit PDE5 may vary depending upon the compound's chemical structure. SMF ¶ 36; *see also* Ex. 3, Rotella Noninfringement Decl. at ¶¶ 106-118; App. at 0074-0080. The more tightly a compound binds PDE5, the higher the affinity it is considered to have for PDE5. *Id.* Due to its uniquely different molecular structure, tadalafil achieves substantially different results from those achieved by zaprinast and MY5445, as demonstrated by each compound's respective affinity for PDE5 or selectivity for PDE5 versus other PDEs. SMF ¶¶ 38-46; *see also* Ex. 3, Rotella Noninfringement Decl. at ¶¶ 106-118; App. at 0074-0080. In particular, the literature demonstrates that tadalafil is 13 times more potent for PDE5 than zaprinast, while zaprinast is 4 times more potent for PDE5 than MY5445. SMF ¶¶ 40, 44.

3. Due to Its Uniquely Different Structure, Tadalafil Achieves Substantially Different Results In Its Selectivity For PDE5 Versus Other PDE Enzymes

A further substantial difference between tadalafil and zaprinast, MY5445, or any other compound disclosed in the '124 Patent is with regard to its selectivity for a particular PDE enzyme. Here, the selectivity of a compound is important in determining its clinical relevance and therapeutic efficacy as a PDE5 inhibitor. The higher the affinity of a compound for a given receptor relative to other potential receptor sites, the greater the selectivity of that compound. SMF ¶ 37; *see also* Ex. 3, Rotella Noninfringement Decl. at ¶¶ 106-118; App. at 0074-0080. Thus, selectivity measures the affinity of a compound to PDE5 relative to other PDEs, and is often a key factor in determining a compounds's side-effect profile. *Id.*

Tadalafil's selectivity profile is very different from zaprinast. SMF ¶¶ 38-46; *see also* Ex. 3, Rotella Noninfringement Decl. at ¶¶ 106-118; App. at 0074-0080. Zaprinast has selectivity for

PDE6—a characteristic that has been linked to vision problems. SMF ¶¶ 41-42. In contrast, tadalafil has been found to be significantly more selective for PDE5 than PDE6, which is a result in the body that likely explains why tadalafil has no vision problems reported with its clinical use. *Id.* For a drug taken once a day (the indication for treating signs and symptoms of BPH), this is a substantial difference in results from not only the other disclosed compounds in the '124 Patent but from all other known PDE5 inhibitors. *Id.*; *see also* Ex. 3, Rotella Noninfringement Decl. at ¶¶ 115-116; App. at 0078-0079.

Zaprinast also is selective for PDE1, PDE9 and PDE10, whereas tadalafil has no selectivity for those PDEs as evidenced by its lack of any measurable potency for those PDEs. SMF ¶ 40. Furthermore, Tadalafil is five times more potent for PDE11 than zaprinast. *Id.*

A reasonable search of the literature did not uncover any PDE selectivity data for MY5445 that could be compared to that of tadalafil. SMF ¶ 45. However, given the reported data in the literature on tadalafil and the significant structural differences between tadalafil and MY5445, it would be reasonable to expect that tadalafil's selectivity for PDE5 compared to other PDEs would be substantially different from MY5445's selectivity profile. SMF ¶¶ 44-45.

4. Due To Its Uniquely Different Structure, Tadalafil Achieves Uniquely Different And Clinically Important Pharmacokinetic Results

In addition to tadalafil's different enzyme interaction and inhibition profile, tadalafil's different pharmacokinetic profile further demonstrates why the differences between tadalafil, zaprinast, and MY5445 are substantial. SMF ¶¶ 47-51; *see also* Ex. 3, Rotella Noninfringement Decl. at ¶¶ 119-122; App. at 0080-0081. The pharmacokinetic (PK) profile of a compound describes the movement of a drug within and around the body, including its entry into body tissues and cells, metabolism, and elimination or excretion.

There is no evidence in the literature or the record in this case showing a pharmacokinetic profile for either zaprinast or MY5445 that is the substantially the same as the pharmacokinetic profile for tadalafil. *Id.* Moreover, given the substantially different chemical structures as compared to tadalafil (e.g., zaprinast and MY5445 both have bicyclic core structures, whereas tadalafil has a rigid tetracyclic core structure), the pharmacokinetic data for either zaprinast or MY5445 would be expected to differ greatly from tadalafil's pharmacokinetic data. *Id.* The pharmacokinetic data of tadalafil compared to sildenafil is demonstrative of these expected differences—most notably, tadalafil's significantly longer half-life and greater AUC. SMF ¶ 49; *see also* Ex. 3, Rotella Noninfringement Decl. at ¶ 121-22; App. at 0080-0081.

The different results achieved in tadalafil's enzyme inhibition profile and pharmacokinetic profile are substantial and clinically important in the context of tadalafil's use for BPH. SMF ¶¶ 50-51; *see also* Ex. 3, Rotella Noninfringement Decl. at ¶¶ 115-16; App. at 0078-0079. Tadalafil's significantly longer half-life and greater AUC may be valuable to longer therapeutic effect, which is ideal for managing conditions, like BPH, which may require continuous drug activity, as opposed to a transitory condition like a headache. *Id.* Tadalafil is the only compound currently approved by the FDA to treat BPH; none of the compounds disclosed in the '124 Patent—including sildenafil (Viagra)—have been approved to treat BPH. *Id.* Zaprinast and MY5445 have never been approved for any clinical use.

E. Because Tadalafil Was Known As Of The Filing Date For The '124 Patent, UroPep Is Estopped From Asserting A Doctrine Of Equivalents Argument.

As discussed above, UroPep cannot meet its burden of showing literal infringement of the '124 Patent claims because tadalafil is not "equivalent" to the corresponding disclosed structures of § 112, ¶ 6. UroPep also cannot avail itself of the Doctrine of Equivalents to avoid summary judgment of noninfringement.

As explained by the Federal Circuit in *Chiuminatta*:

> Both § 112, ¶ 6, and the doctrine of equivalents protect the substance of a patentee's right to exclude by preventing mere colorable differences or slight improvements from escaping infringement, the former, by incorporating equivalents of disclosed structures into the literal scope of a functional claim limitation, and the latter, by holding as infringements equivalents that are beyond the literal scope of the claim. They do so by applying similar analyses of insubstantiality of the differences. Thus, a finding of a lack of literal infringement for lack of equivalent structure under a means-plus-function limitation may preclude a finding of equivalence under the doctrine of equivalents.

145 F.3d at 1310.

The Court in *Chiuminatta* went on to point out an important difference, however: "The doctrine of equivalents is necessary because one cannot predict the future." *Id.* As in *Chiuminatta*, the accused structure of tadalafil involves technology that predates the purported invention claimed in the '124 Patent itself. Tadalafil was disclosed as a compound able to inhibit PDE5 in PCT Application no. PCT/EP95/00183, published on July 27, 1995—nearly two years before the first filing date of the parent application to the '124 patent. In such a case, "a finding of non-equivalence for § 112, ¶6, purposes should preclude a contrary finding under the doctrine of equivalents." *Id.* At 1311. As explained by the Court, "[t]his is because, as we have already determined, the structure of the accused device differs substantially from the disclosed structure, and given the prior knowledge of the technology asserted to be equivalent, it could readily have been disclosed in the patent." *Id.* Thus, "[t]here is no policy-based reason why a patentee should get two bites at the apple. If he or she could have included in the patent what is now alleged to be equivalent, and did not, leading to a conclusion that an accused device lacks an equivalent to the disclosed structure, why should the issue of equivalence have to be litigated a second time?" *Id.*

Because UroPep cannot show that tadalafil is an "equivalent" to zaprinast or MY5445 (or any compound disclosed in the '124 Patent) for purpose of literal infringement under § 112, ¶ 6,

UroPep also cannot use the doctrine of equivalence to avoid summary judgment of noninfringement. "An element of a device cannot be 'not equivalent' and equivalent to the same structure." *Id.* In addition, because tadalafil was known well before the filing date of the '124 Patent application (SMF ¶ 21), UroPep is barred from using the doctrine of equivalence to get "two bites at the apple."

VI. CONCLUSION

For the foregoing reasons, summary judgment of noninfringement should be granted for Defendants.

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CERTIFICATE OF SERVICE

The undersigned certifies that the foregoing document was filed electronically in compliance with Local Rule CV-5(a). As such, this motion was served on all counsel who are deemed to have consented to electronic service. Local Rule CV-5(a)(3)(A). Pursuant to Fed. R. Civ. P. 5(d) and Local Rule CV-5(d) and (e), all other counsel of record not deemed to have consented to electronic service were served with a true and correct copy of the foregoing by email and/or fax, on this the 22nd day of July, 2016.

/s/ Jon B. Hyland
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